Appeal No. 2017-2513

United States Court of Appeals

for the

Federal Circuit

SUPERNUS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

– v. –

TWI PHARMACEUTICALS, INC., TWI INTERNATIONAL LLC, d/b/a TWI PHARMACEUTICALS USA,

Defendants-Appellants.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY IN NO. 1:15-CV-00369-RMB-JS, JUDGE RENÉE MARIE BUMB

NONCONFIDENTIAL BRIEF FOR PLAINTIFF-APPELLEE

February 9, 2018

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Exela PharmSci Inc., 780 F.3d 1364, 1368 (Fed. Cir. 2015) ("Infringement . . . is a question of fact that we review for clear error."); *Allergan Sales, LLC v. Sandoz, Inc.*, No. 2017-1499, 2017 WL 6547648, at *2 (Fed. Cir. Dec. 22, 2017) (nonprecedential) ("Whether a claim satisfies the written description requirement is a question of fact that, on appeal from a bench trial, we review for clear error."); *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1370-72 (Fed. Cir. 2017) (reviewing subsidiary factual findings in the indefiniteness context for "clear error").

TWi has failed to demonstrate any clear error in the district court's opinion, which was rendered after considering voluminous documentary evidence and weighing the testimony and credibility of three fact witnesses and five expert witnesses. *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012) ("Credibility determinations by the trial judge can virtually never be clear error.") (citation omitted).

I. TWi's Tablets Contain a "homogeneous matrix"

The claims of the Patents-in-Suit require a pharmaceutical formulation wherein four ingredients (elements 1(a)-1(d)) are contained

required blend-uniformity testing, FDA-required content-uniformity testing, FDA-required dissolution testing, and chemical imaging.

ARGUMENT

I. The District Court Committed No Clear Error in Finding that TWi's Tablets Satisfy the "homogeneous matrix" Claim Limitation

The claims of the Patents-in-Suit require a "homogeneous matrix" comprising elements 1(a)-(d). (*See, e.g.*, Appx159-160, claim 1). The district court construed the "homogeneous matrix" claim limitation to mean a "matrix in which the ingredients or constituents are uniformly dispersed." (Appx2492; Appx3492-3496).

The district court found that TWi's Tablets comprise a homogeneous matrix (i.e., a uniform dispersion of matrix ingredients) based on TWi's manufacturing process, FDA-required uniformity testing, and chemical images. (Appx26-52). The district court committed no clear error in reaching this purely factual conclusion. *Cadence*, 780 F.3d at 1368 ("A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made.").

Raman chemical analysis is inappropriate for assessing or confirming the homogeneity of the tablet matrix." (Appx51-52).

TWi also argues that Dr. Bugay tested an expired tablet in his chemical-imaging experiments. (Br. at 27). TWi's Tablets, however, do not currently have an FDA-approved expiration date. (Appx49). Rather, TWi's Tablets have "a proposed expiration date based only upon accelerated stability studies, which may be extended by the FDA after review of TWi's full-term stability data." (Appx49). Nevertheless, the district court found that Dr. Bugay "credibly testified that he did not observe any evidence of degradation or impurities in the sample TWi Tablet that would have impacted the accuracy of his Raman chemical images," and that any such degradation "would have been readily apparent to him." (Appx49).

Dr. Bugay's images of TWi's tablet confirm the district court's homogeneity findings.

D. The District Court Consistently and Properly Applied Its Definition of "homogeneous matrix"

TWi accuses the district court of applying varying definitions of "homogeneous matrix" and misapplying those definitions. (Br. at 55-57, 61-62). It did not.

2017 WL 6547648
Only the Westlaw citation is currently available.
This case was not selected for
publication in West's Federal Reporter.
See Fed. Rule of Appellate Procedure 32.1
generally governing citation of judicial
decisions issued on or after Jan. 1, 2007.
See also U.S.Ct. of App. Fed. Cir. Rule 32.1.
United States Court of Appeals,
Federal Circuit.

ALLERGAN SALES, LLC, Plaintiff-Cross-Appellant
v.
SANDOZ, INC., Alcon Laboratories, Inc.,
Alcon Research, Ltd., Defendants-Appellants

2017-1499
|
2017-1500
|
2017-1558
|
2017-1559
|
Decided: December 22, 2017

Appeals from the United States District Court for the Eastern District of Texas in Nos. 2:12-cv-00207-JRG, 2:15-cv-00347-JRG, Judge J. Rodney Gilstrap.

Attorneys and Law Firms

JONATHAN ELLIOT SINGER, Fish & Richardson, PC, San Diego, CA, argued for plaintiff-cross-appellant. Also represented by SUSAN E. MORRISON, ROBERT M. OAKES, Wilmington, DE; DEANNA JEAN REICHEL, Minneapolis, MN.

JOHN C. O'QUINN, Kirkland & Ellis LLP, Washington, DC, argued for defendants-appellants. Also represented by SEAN M. MCELDOWNEY, CALVIN ALEXANDER SHANK; BRYAN SCOTT HALES, Chicago, IL.

Before Moore, Mayer, and Hughes, Circuit Judges.

Opinion

Hughes, Circuit Judge.

***1** Allergan Sales, LLC sued generic drug manufacturers under the Hatch-Waxman Act, alleging infringement of U.S. Patent Nos. 7,030,149, 7,320,976, and 8,748,425. The U.S. District Court for the Eastern District of Texas found the asserted claims not invalid but only claims of the '425 patent infringed. We find no reversible error in the district court's finding of no invalidity. Nevertheless, because we find that the accused proposed generic drug contemplates administering dosages of a specific composition that is not claimed in any of the patents, we affirm-in-part and reverse-in-part.

I

Allergan holds the approved new drug application for Combigan®, which is used to lower intraocular pressure in glaucoma and ocular hypertension patients. Combigan® is a "fixed combination" ophthalmic solution consisting of 0.2% brimonidine tartrate and 0.68% timolol maleate for twice-daily dosage.

Allergan claims that the '149, '976, and '425 patents cover Combigan®. These patents share a common specification, which describes: (1) a "Brimonidine Tartrate 0.20% (w/v)" and "Timolol Maleate 0.68% (w/v) (Equivalent to 0.50% (w/v) timolol)" pharmaceutical composition; and (2) a clinical study using that composition for twice daily administration. *See, e.g.*, J.A. 347–50. In particular, Allergan claims that claim 4 of the '149 patent, claim 1 of the '976 patent, and claims 1–8 of the '425 patent protect Combigan® and its administration.

Claim 4 of the '149 patent recites a method of reducing the number of daily administrations of 0.2% brimonidine and 0.5% timolol in a single composition from three times a day to two times a day "without loss of efficacy." J.A. 350.

Claim 1 of the '976 patent recites a method of administering "a therapeutically effective amount" of composition comprising 0.2% brimonidine and 0.5% timolol twice daily. J.A. 356.

Claim 1 of the '425 patent recites administering twice daily a single combination comprising 0.2% brimonidine tartrate and 0.5% timolol free base to "reduce[ ] the incidence of one or more adverse events" listed in the claim. J.A. 366. Claims 2–8 of the patent depend from

claim 1, each specifically reciting only one of the adverse events enumerated in claim 1. *Id.*

Sandoz, Inc., Alcon Laboratories, Inc., and Alcon Research, Ltd. (collectively, Sandoz) filed and maintained an abbreviated new drug application (ANDA) with the U.S. Food and Drug Administration, seeking its approval to market generic versions of Combigan®. Allergan sued Sandoz for direct, induced, and contributory infringement, asserting numerous patents in three different actions, only the last two of which proceeded to a consolidated bench trial on the '149, '976, and '425 patents.

The district court found the asserted claims of the patents not invalid as obvious. The court also found that claim 4 of the '149 patent satisfies the written description requirement. The court finally determined that Sandoz's ANDA does not infringe claim 4 of the '149 patent or claim 1 of the '976 patent, but does infringe claims 1–8 of the '425 patent.

***2** Sandoz appeals the district court's no-invalidity and infringement determinations. Allergan cross-appeals the finding of non-infringement. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II

We review the district court's legal determinations de novo and factual findings for clear error. *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1358 (Fed. Cir. 2014). Obviousness is a question of law that we review de novo, and we review any underlying factual questions for clear error. *Honeywell v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). "Whether a claim satisfies the written description requirement is a question of fact that, on appeal from a bench trial, we review for clear error." *Alcon Res. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). Infringement is a question of fact that we review for clear error. *Id.* at 1186.

A

Sandoz first argues that all asserted claims are invalid as obvious. A claim is invalid if, at the time the invention was disclosed, a person having ordinary skill in the art would have found the patented invention obvious in light of the prior art. *See* 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415–16, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). But patents are presumed to be valid and overcoming that presumption requires clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95, 131 S.Ct. 2238, 180 L.Ed.2d 131 (2011).

The district court found the asserted claims not invalid as obvious, reasoning that Sandoz presented substantially the same arguments and evidence in an earlier dispute with Allergan in which we held that claim 4 of the '149 patent recited an efficacy limitation that is neither suggested nor inherent in any prior art in the record. J.A. 74–76; *see also Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293–94 (Fed. Cir. 2013). Relying on that precedential decision, the court found that all asserted claims recited analogous efficacy limitations, neither suggested nor inherent in prior art produced by Sandoz. J.A. 163.

Sandoz contends that the court erred because the asserted claims merely recite the inherent results of administering an obvious combination. We disagree. As we concluded in the earlier dispute regarding claim 4 of the '149 patent, the concomitant administration of brimonidine and timolol ophthalmic composition twice daily is obvious in view of the prior art. *See* J.A. 122–25; *Allergan*, 726 F.3d at 1294. Each asserted claim, however, expressly recites an additional efficacy limitation that further restricts the method of administering the composition twice daily: (1) "without loss of efficacy" in claim 4 of the '149 patent, *see* J.A. 350; (2) "a therapeutically effective amount" in claim 1 of the '976 patent, *see* J.A. 356; and (3) "reduc[ing] the incidence of one or more adverse events" in claim 1 of the '425 patent,[1] *see* J.A. 366. *See also Allergan*, 726 F.3d at 1293. Those efficacy limitations are not disclosed by any prior art reference in the record. To the contrary, the prior art shows that the combination dosed twice daily produces a loss of efficacy in the afternoon. J.A. 107–116; *see also Allergan*, 726 F.3d at 1294. The efficacy limitations are also not inherent in the administration of the ophthalmic composition, a finding adequately supported by the record. *See, e.g.*, J.A. 2572–75, 3007–09, 3117–19, 3243–45. Accordingly, the asserted claims merely recite those administrations of the composition that satisfy the efficacy limitations—but not those that end up in, for example, a loss of efficacy, examples of which abound in the prior art offered by Sandoz.

780 F.3d 1364
United States Court of Appeals,
Federal Circuit.

CADENCE PHARMACEUTICALS INC.
SCR Pharmatop, Plaintiffs–Appellees
v.
EXELA PHARMSCI INC., Exela Holdings Inc., Exela Pharma Sciences LLC, Defendants–Appellants.

No. 2014–1184.
|
March 23, 2015.

Synopsis

Background: Owner and exclusive licensee commenced action against competitor, alleging infringement of patents relating to formulations and methods for making liquid acetaminophen compositions. The United States District Court for the District of Delaware, Leonard P. Stark, J., 886 F.Supp.2d 445, construed the claims, and ruled that competitor infringed certain asserted claims of both patents and failed to prove invalidity. Competitor appealed.

Holdings: The Court of Appeals, Linn, Circuit Judge, held that:

[1] statement in specification that concentration of buffer "may be" between 0.1 and 10 mg-ml was not limiting;

[2] sodium ascorbate present in accused formulation as antioxidant met buffering agent limitation;

[3] accused process infringed under equivalents doctrine;

[4] statements made during prosecution did not rise to level of explicit disclaimer; and

[5] patent was not obvious.

Affirmed.

West Headnotes (16)

[1] Patents
Obviousness;lack of invention
Patents
Construction and Operation of Patents

When reviewing questions of patent claim construction and obviousness, the Court of Appeals reviews underlying factual determinations for clear error and ultimate determinations de novo. 35 U.S.C.A. § 103(a).

2 Cases that cite this headnote

[2] Patents
Infringement or noninfringement

Patent infringement, either literal or under the equivalents doctrine, is a question of fact that is reviewed for clear error when tried without a jury.

Cases that cite this headnote

[3] Federal Courts
Definite and firm conviction of mistake

A factual finding is clearly erroneous if, despite some supporting evidence, a reviewing court is left with the definite and firm conviction that a mistake has been made.

Cases that cite this headnote

[4] Patents
Questions of law or fact

Whether the patent equivalents doctrine would vitiate a claimed element is a question of law that is reviewed de novo.

4 Cases that cite this headnote

[5] Patents
Specifications and Drawings;Written Description
Patents

In this Hatch–Waxman Act litigation, Exela PharmSci Inc., Exela Holdings, Inc. and Exela Pharm Sciences, LLC (collectively "Exela") appeal the district court's construction of certain claim terms of U.S. Patents No. 6,028,222 (the "#222 patent") and No. 6,992,218 (the "#218 patent"), *Cadence Pharm., Inc. v. Paddock Labs. Inc.,* 886 F.Supp.2d 445 (D.Del.2012), and its rulings that Exela infringed certain asserted claims of both patents and failed to prove invalidity as to the #218 patent. *Cadence Pharm., Inc. v. Exela Pharma Scis., LLC,* No. 11–733–LPS, 2013 U.S. Dist. LEXIS 166097 (D.Del. Nov. 14, 2013). For the reasons set forth *infra,* we affirm.

I. BACKGROUND

A. The Patents–In–Suit

SCR Pharmatop and Cadence Pharmaceuticals, Inc. (collectively "Cadence") are the owner and exclusive licensee, respectively, of the #222 and #218 patents. These patents are directed to aqueous phenol formulations —particularly acetaminophen (sometimes referred to as "paracetamol"). #222 patent abstract; #218 patent abstract, col.1 ll.32–33.

The #222 patent issued on February 22, 2000. It explains that in aqueous solutions, acetaminophen decomposes into potentially toxic products. *See* # 222 patent col.1 ll.16–22, ll.45–48. The #222 patent is directed at avoiding this decomposition by adding a free-radical capturing agent and a buffer. *Id.* abstract. Claim 1 of the #222 patent is the only independent claim, and recites (with the disputed term highlighted):

> 1. A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing *a buffering agent* and at least one member of the group consisting of a free radical scavenger and a radical antagonist.

The #218 patent claims priority to a French application filed on June 6, 2000. The #218 patent discloses a method for obtaining stable acetaminophen formulations by deoxygenating solutions with an inert gas to achieve oxygen concentrations below 2 parts-per-million ("ppm"). #218 patent abstract, col.1 ll.32–33. Claim 1 of the #218 patent is the only independent claim, and recites (with the edits from the certificate of correction in brackets and the disputed terms highlighted):

> 1. A method for preparing an *aqueous solution* with an active [principle of phenolic] nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising de-oxygenation of the *solution* by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm, and *optionally* the aforementioned *aqueous solution* with an active principle is *topped with an inert gas atmosphere heavier than air and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum,* and the oxygen content of *the aqueous solution* is below 2 ppm, and optionally the deoxygenation of the *solution* is completed by addition of an antioxidant.

***1368** B. History of the Dispute

Cadence Pharmaceuticals Inc. markets an injectable acetaminophen product, which is approved by the Food and Drug Administration ("FDA") and is distributed under the name Ofirmev®. The FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (better known as the "Orange Book") lists the #222 and #218 patents in connection with Ofirmev®.

Exela filed an Abbreviated New Drug Application ("ANDA") with the FDA, seeking approval of a generic equivalent of Ofirmev®. The ANDA included a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2012) (commonly referred to as a "Paragraph IV certification") stating that the #222 and # 218 patents were invalid and not infringed. In response, Cadence sued Exela for infringing claims 1, 3, 4, 5, 9, 10, 12 and 16–18 of the #222 patent and claims 1, 3, 4 and 19 of the #218 patent pursuant to 35 U.S.C. § 271(e)(2) (2012).

KeyCite Yellow Flag - Negative Treatment
Declined to Extend by Apple, Inc. v. Samsung Electronics Co., Ltd., N.D.Cal., July 1, 2012

664 F.3d 922
United States Court of Appeals,
Federal Circuit.

CELSIS IN VITRO, INC., Plaintiff–Appellee,
v.
CELLZDIRECT, INC., and Invitrogen Corporation, Defendants–Appellants.

No. 2010–1547.
|
Jan. 9, 2012.

Synopsis
Background: Patentee brought action against competitor alleging infringement of patent related to methods for making and using multi-cryopreserved hepatocytes. The United States District Court for the Northern District of Illinois, Milton I. Shadur, J., granted patentee's motion for preliminary injunction. Competitor appealed.

Holdings: The Court of Appeals, Rader, Chief Judge, held that:

[1] district court did not abuse its discretion in finding that patentee had shown likelihood of success on nonobviousness;

[2] court did not abuse its discretion in finding that patentee had shown likelihood that it would irreparably harmed;

[3] court did not abuse its discretion in finding that balancing of harms tilted heavily in patentee's favor; and

[4] court did not abuse its discretion in finding that public interest favored preliminary injunction.

Affirmed.

Gajarsa, Circuit Judge, filed dissenting opinion.

West Headnotes (15)

[1] Federal Courts
Preliminary injunction;temporary restraining order

A district court's decision to grant a motion for preliminary injunction is reviewed for an abuse of discretion.

2 Cases that cite this headnote

[2] Federal Courts
Abuse of discretion in general

To constitute an abuse of discretion, a district court decision must either make a clear error of judgment in weighing relevant factors or exercise discretion based upon an error of law.

Cases that cite this headnote

[3] Injunction
Grounds in general;multiple factors

A district court analyzes four factors when considering a preliminary injunction: (1) likelihood of success on the merits, (2) irreparable harm, (3) balance of hardships, and (4) public interest.

12 Cases that cite this headnote

[4] Patents
Establishment of validity and enforceability of patent

District court did not abuse its discretion in finding that patentee had shown likelihood of success on nonobviousness, on motion for preliminary injunction in action against competitor alleging infringement of patent related to methods for making and using multi-cryopreserved hepatocytes, where, among other things, invention was in art well-known for its unpredictability, art was crowded field for many years and yet there was not one reference to multi-cryopreservation, and prior art taught away from multiple freezings. 35 U.S.C.A. § 103.

With respect to the de Sousa article, this court sees no error in the district court's reliance on Dr. Strom's testimony that de Sousa does not describe or suggest more than one round of freezing, nor does it describe or suggest pooling. Instead, de Sousa only discloses a single cryopreservation. Even LTC's expert Dr. Gupta did not testify that de Sousa discloses multi-cryopreservation. This court has not seen LTC identify any teaching, suggestion, or motivation in the de Sousa article that multiple rounds of freezing would somehow increase rather than decrease cell viability. Instead, to make this leap, LTC makes vague references to "market need" and testimony from its witnesses Dr. Gupta and Dr. Albert Li. Without more, this reference to "market need," properly linked to the claimed invention, is actually probative of long felt need under objective criteria analysis and supportive of non-obviousness.

***929** Dr. Gupta opined on a "more resistance" theory, and Dr. Li opined on a "mathematical calculation" theory. Specifically, Dr. Gupta (opining specifically on the de Sousa article) claimed that cells that survived the first freeze would be "more resistant" and therefore more likely to survive a second freeze. Dr. Li (opining generally, not specifically on the de Sousa article) claimed that the same number of cells that survived the first freeze would survive the second freeze. The de Sousa article does not disclose either of these hindsight theories.

[6] **[7]** The district court did not find the testimony of LTC's experts Dr. Gupta and Dr. Li credible. The district court has wide discretion to weigh expert credibility. *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.,* 460 F.3d 1349, 1362–63 (Fed.Cir.2006) ("As for the relative weight given to the testimony of both sides' expert witnesses, we accord the trial court broad discretion in determining credibility because the court saw the witnesses and heard their testimony.") (quoting *Energy Capital Corp. v. United States,* 302 F.3d 1314, 1329 (Fed.Cir.2002)); *Bristol–Myers Squibb Co. v. Rhone–Poulenc Rorer, Inc.,* 326 F.3d 1226, 1236 (Fed.Cir.2003) ("Moreover, the district court did not find convincing or credible the opinion of RPR's expert.... [T]he district court is best suited to make credibility determinations, and we accord such determinations deference.") (citing *Refac Int'l, Ltd. v. Lotus Dev. Corp.,* 81 F.3d 1576, 1582 (Fed.Cir.1996)). This court defers to such credibility determinations. *Nilssen v. Osram Sylvania, Inc.,* 504 F.3d 1223, 1231–32 (Fed.Cir.2007) ("While an opposite conclusion could have been reached, it is not the function of a court of appeals to override district court judgments on close issues, where credibility findings have been made."); *Agfa Corp. v. Creo Prods. Inc.,* 451 F.3d 1366, 1379 (Fed.Cir.2006) ("This court must defer heavily to the trial court's credibility determinations.... Credibility determinations by the trial judge can virtually never be clear error.") (quoting *JVW Enters., Inc. v. Interact Accessories, Inc.,* 424 F.3d 1324, 1334 (Fed.Cir.2005)). Thus, these determinations of credibility also buttress the record for nonobviousness.

Here, the district court found that the LTC expert's "revisionist history is unpersuasive." Hr'g Tr. 10:7–8; *see also* Hr'g Tr. 7:11–13 ("Instead of a more candid 'Why didn't I think of that,' we get [LTC arguing] 'Anybody reasonably skilled in the art would have thought of that.' "). Not one of LTC's experts testified to actually performing the claimed process or documenting their alleged understanding before the time of the invention, despite having the financial, scientific, and professional incentive to do so. The district court found that LTC's experts did not predict the results of the claimed methods at the time of the invention, nor could they find any reference in the prior art suggesting that any other scientist had. Hr'g Tr. 7:23–8:1 ("That was not the subject of numerous articles authored or assembled by Dr. Li or Dr. Gupta or by any of the other scientists who participated in the consortium about which Dr. Li testified, or for that matter by anybody else."). Accordingly, in this preliminary injunction context, this court determines that the district court did not clearly err in finding a person of ordinary skill in the art likely would not have found the invention obvious either.

In sum, the record supports the district court's conclusion that Celsis has shown a likelihood of success that a person of ordinary skill in the art would not have considered the claimed methods obvious at the time of the invention.

***930** IV.

[8] **[9]** The district court found that Celsis would suffer irreparable harm absent a preliminary injunction. As the district court recognized, the simple fact that one could, if pressed, compute a money damages award does not always preclude a finding of irreparable harm. As its name implies, the irreparable harm inquiry seeks to measure harms that no damages payment, however great, could address. *See Altana Pharma AG v. Teva Pharm.*

845 F.3d 1357
United States Court of Appeals,
Federal Circuit.

ELI LILLY AND COMPANY, Plaintiff-Appellee
v.
TEVA PARENTERAL MEDICINES, INC., APP Pharmaceuticals LLC, Pliva Hrvatska D.O.O., Teva Pharmaceuticals USA, Inc., Barr Laboratories, Inc., Defendants-Appellants

2015-2067
|
Decided: January 12, 2017

Synopsis

Background: Patentee brought infringement action against generic drug manufacturers, alleging infringement of patent describing method of administering a chemotherapy drug, pemetrexed disodium, with vitamins. The district court determined after bench trial that patent was valid, 2014 WL 1350129, and manufacturers appealed. Parties stipulated to remand, and the Court of Appeals, 567 Fed.Appx. 967, remanded. On remand, the United States District Court for the Southern District of Indiana, Tanya Walton Pratt, J., 126 F.Supp.3d 1037, granted judgment for patentee after bench trial. Manufacturers appealed.

Holdings: The Court of Appeals, Prost, Chief Judge, held that:

[1] physicians conditioned pemetrexed treatment on folic acid pretreatment, as required on induced infringement claim for method in proposed product labeling to directly infringe;

[2] physicians established manner or timing of performance, as required on induced infringement claim for method in proposed product labeling to directly infringe;

[3] method in proposed product labeling encouraged, recommended, or promoted infringement, as required for liability on induced infringement claim;

[4] "vitamin B12" limitation was not indefinite;

[5] prior art did not disclose claimed doses and schedules of vitamin B12 for purposes of pemetrexed pretreatment, and thus method patent claim was not invalid as obvious; and

[6] method patent claim was not invalid on claim of obviousness-type double patenting over claim in prior art that disclosed use of much greater amount of folic acid with antifolate administered to mammal.

Affirmed.

West Headnotes (30)

[1] Patents
Inducement to infringe

Liability for induced patent infringement must be predicated on direct infringement; the patentee also must show that the alleged infringer possessed the requisite intent to induce infringement, which requires that the alleged infringer knew or should have known his actions would induce actual infringements. 35 U.S.C.A. § 271(b).

4 Cases that cite this headnote

[2] Patents
Degree of proof

A patentee seeking relief on the basis of induced infringement under the statute governing submission of abbreviated new drug applications (ANDA) for patented drugs bears the burden of proving infringement by a preponderance of the evidence. 35 U.S.C.A. § 271(e)(2).

Cases that cite this headnote

[3] Patents

covered by the asserted claims, and Eli Lilly does not need to rely on speculation about physician behavior.

Again, the product labeling includes repeated instructions and warnings regarding the importance of and reasons for folic acid treatment, and there is testimony that the Physician Prescribing Information, as the name indicates, is directed at physicians. *See* J.A. 2181, 11253, 11255, 11256, 11258, 11278. The instructions are unambiguous on their face and encourage or recommend infringement.

Defendants rely heavily on evidence that physicians as a matter of practice take steps beyond the instructions in the product labeling, such as asking patients to keep pill diaries or pill counts, or confirming compliance with folic acid administration. For example, they point to Dr. Chabner's testimony that he gives patients instructions "beyond what the instruction is in th[e] patient information." J.A. 2235–36. But the asserted claims do not recite additional steps such as pill diaries, pill counts, and compliance measures. Where the product labeling already encourages infringement of the asserted claims, as it does here, a physician's decision to give patients even more specific guidance is irrelevant to the question of inducement. [7]

In sum, evidence that the product labeling that Defendants seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement. The district court did not clearly err in concluding that Defendants would induce infringement of the asserted claims of the '209 patent.

II

[12] We turn next to the district court's holding that the limitation "vitamin B12" was not indefinite. Pursuant to 35 U.S.C. § 112, ¶ 2, a patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." [8] The district ***1370** court considered the indefiniteness of the asserted claims before the Supreme Court changed the relevant standard in *Nautilus, Inc. v. Biosig Instruments, Inc.*, —— U.S. ——, 134 S.Ct. 2120, 189 L.Ed.2d 37 (2014), and held that "vitamin B12" was not indefinite. [9] *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.* (*Eli Lilly I*), No. 1:10–cv–1376–TWP–DKL, 2012 WL 2358102, at *11–12 (S.D. Ind. June 20, 2012). The district court further construed "vitamin B12" to mean "cyanocobalamin," a particular vitamin supplement. *Id.* at *12.

[13] **[14]** In *Nautilus*, the Supreme Court rejected our "not amenable to construction or insolubly ambiguous" standard for indefiniteness and articulated, instead, that "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." 134 S.Ct. at 2124. Indefiniteness is a question of law that we review de novo. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). We have reiterated post-*Nautilus* that "general principles of claim construction apply" to the question of indefiniteness. *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377 (Fed. Cir. 2015) (internal quotation marks omitted). Accordingly, we review subsidiary factual determinations made by the district court based on extrinsic evidence for clear error. *Id.*; *see also Teva*, 789 F.3d at 1341–42 (reviewing subsidiary factual findings in the indefiniteness context for clear error).

The parties do not dispute that, depending on the context, "vitamin B12" can be used in the art to refer either to cyanocobalamin specifically or, more broadly, to a class of compounds including pharmaceutical derivatives of cyanocobalamin. The parties do not dispute that the written description of the '209 patent uses the term both ways. [10] Defendants argue that, because "vitamin B12" is used in two different ways in the intrinsic record, "it is impossible to determine" which meaning applies to the claims "with any reasonable certainty," as required by *Nautilus*. Appellants' Opening Br. 31. Eli Lilly counters that the claims of the '209 patent "involve administering a vitamin B_{12} supplement to a patient," and in that context, "the one and only meaning" of vitamin B_{12} to a person of ordinary skill is cyanocobalamin. Appellee's Br. 35.

[15] **[16]** The district court expressly "accept[ed]" the testimony of Eli Lilly's expert, Dr. O'Dwyer, who concluded that a person of ordinary skill would understand "vitamin B12" to mean cyanocobalamin in the context of the patent claims. *Eli Lilly I*, 2012 WL 2358102, at *11. We do not defer to Dr. O'Dwyer's "ultimate conclusion ***1371** about claim meaning in the context of th[e] patent," as that is a legal question. *Teva*, 789 F.3d

amount of each constituent in any given position, but instead simply measured the probability of the presence or absence of the constituent *at all* in a given sector. Dr. Bugay's Raman imaging results represent the presence or absence of a particular ingredient or constituent as a colored pixel. (Appx8068.) The pixels containing color represented the "probability/concentration" of a detectable amount of a particular constituent in that given pixel. (Appx8104.) There is a *relativistic* (i.e., not absolute) concentration of the ingredient based on the gradient and the shades of the color. (*Id.*) The lighter shade represents a lower *relative* concentration. (*Id.*) Nothing in the Raman testing measured the actual amount of a given constituent in any given location in the expired tablet. Neither was the concentration range between the darkest and lightest shade evaluated.

Although Raman imaging can show the absolute amount of the drug components throughout the tablet ("be made qualitative"), Dr. Bugay did not do "the appropriate work to set up the standards that are necessary to quantitate the various ingredients." (Appx8314.) Dr. Bugay testified that he did not do so because such work would be "extensive." (Appx8105.) And even if Dr. Bugay had done quantitative testing, Dr. Bugay did not test TWi's ANDA product. Instead, he tested an expired sample. (Appx8103.)

B. The District Court's Numerous Conflicting Definitions of "Homogeneous Matrix" Reveal the Indefiniteness of the Term.

The term "homogeneous matrix" has been defined and construed by both the patentee and the district court several times. Neither the parties nor the district court have ever denied that homogeneity is necessarily a matter of degree. (*See e.g.*, Appx89 ("The Court agrees that homogeneity comes in degrees.").) Each construction, however, failed to resolve what degree of homogeneity was required to distinguish between a uniform and non-uniform matrix.

During claim construction, Supernus' expert testified that a POSA would not understand the term "homogeneous matrix" to require perfect molecular uniformity, even though it was achievable. (Appx2334-2335.) Instead, Supernus proposed a construction of "substantially uniform." (Appx2404-2405.) This lead the district court to wonder, "despite how I construe the claim the parties are going to come back before me and say what does the word 'uniform' mean? And if that's the case, then, gee wiz, what are we doing? I don't know." (Appx2404.)

After this colloquy, the district court issued a construction that required a "matrix in which the ingredients or constituents are uniformly dispersed." (Appx2492.) Despite the district court's concerns stated during the Markman hearing, the court did not provide any description of the court's reasoning or where the line of demarcation could be found between "uniformly dispersed" and "non-uniformly" dispersed. The parties were left—as the district court and

Supernus' counsel had foreseen—to "construe the construction." The term still had no definite meaning.

After the district court's construction, but before the trial in this case, the district court further modified its construction. First, the district court noted in the *Actavis* case that "the ordinary meaning of homogeneous is 'loosely . . . used to describe a mixture or solution composed of two or more compounds or elements that are **uniformly dispersed in each other**.'" *Actavis Inc.*, 2016 WL 527838 at *7 (emphasis added) (quoting *Hawley's Condensed Chemical Dictionary* 655 (15th ed. 2007)). Going further, the district court held in that case that "[t]he specifications of the Patents-in-Suit support a construction that uses the ordinary term of homogeneous without the qualifier, substantially." *Id.* Confusingly, in the same opinion, the district court stated that "[t]he [homogeneous matrix] term was not added to describe the degree of uniformity or homogeneity of the Supernus invention." *Id.* at *10. The district court then modified the construction further, defining "homogeneity" as "no localization of constituents." *Id.* at *18.

At trial in this matter, the district court provided an entirely new construction of the "homogeneous matrix" claim term. In doing so, the Court incorporated its reasoning from the *Actavis* case—a case in which TWi was not a party—but then went further, noting that the "Court agrees that homogeneity comes in degrees." (Appx89.) But after stating what homogeneous means, and

that homogeneity is a matter of degree, the court inexplicably concluded that "a person skilled in the art understands that a tablet comprises a homogeneous matrix so long as the matrix constituents are uniformly dispersed, rather than localized in a discrete portion of the tablet matrix, such as a coating or layer, **regardless of the degree of uniformity achieved**." (Appx90 (emphasis added).)

At a minimum, the district court's revised claim construction impermissibly reads the word "homogeneous" out of the "homogeneous matrix" claim element. *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1355 (Fed. Cir. 2005) (eschewing a construction that "would improperly eliminate the word 'pleasing' from the phrase 'aesthetically pleasing.'").

This new construction also, per the district court's own findings, contradicts a POSA's understanding of the term, which requires a degree of uniformity to be homogeneous. *Seattle Box Co. v. Indus. Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984) ("When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree."). The district court's incorrect re-construction constitutes reversible legal error. *Ferring B.V.*, 764 F.3d at 1411.

disclosed procedures and may "realize it didn't work" before obtaining a homogeneous matrix, as construed. (Appx8334.)

IV. THE DISTRICT COURT FAILED TO APPLY ITS CONSTRUCTION OF THE TERM "HOMOGENEOUS MATRIX."

In analyzing whether Supernus had proven infringement of the asserted claims, the district court erroneously re-construed the term "homogeneous matrix" and Supernus failed to meet its burden of proof under the proper construction. Thus, the district court erred in both steps of its infringement analysis. *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998).

A. The District Court Applied a New "Absence of Localization" Construction Instead of Its "Uniformity" Construction.

At trial, and after TWi had put on a significant amount of evidence regarding the paradox of high sheer granulation, the district court abandoned its uniformity construction and instead only looked for an "absence of localization."

The district court relied on Supernus' experts for this new, ostensibly more lax, construction. In its decision, the district court noted that Supernus' experts opined that "a person would understand that a lack of localization of excipients across the tablet matrix indicates that the matrix constituents are homogeneous," (Appx47), that "matrix homogeneity in this context is measured by lack of localization of any excipient," (Appx48), that the "ANDA Product comprises a

homogeneous matrix because there is no localization of any of the excipients," (*id.*), and finally that "this lack of localization . . . establishes that each TWi Tablet comprises a matrix in which all of the constituents are uniformly dispersed." (*Id.*)

At no point did the district court explain how homogeneity, which per the dictionaries cited by the parties and the district court required uniformity, necessarily equates with an absence of localization. And as discussed above, Supernus admitted this issue during claim construction when it sought a "substantially uniform" definition, arguing in expert declarations that:

> The problem with Defendants' construction is that it does not clarify the required degree of homogeneity or uniformity. . . . **In contrast, my construction reflects a POSA's understanding that homogeneity exists in degrees and that the patents in suit require substantial uniformity.**

(Appx762 (emphasis added).)

B. The Evidence Relied on by the District Court Does Not Prove Uniformity.

Supernus' evidence did not show that the ingredients in TWi's ANDA products were uniformly dispersed within the matrix. On the contrary: (1) Supernus did not consider the impact of vital settings in TWi's specific manufacturing process on the resulting matrix homogeneity, instead relying on the idealized outcome of a generic high-shear wet granulation process; (2) FDA

TABLE 4-continued

Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes

Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Percent Composition for the three exemplary enhanced formulations; CRe-F, CRe-M, and CRe-S.

Formulation	% PD0294-046 CRe-F	% PD0294-051 CRe-M	% PD0294-054 CRe-S
Oxcarbazepine	60	60	60
Prosolv SMCC50	15	10	5
PVP K25	5	5	5
HPMC K4M premium	5	10	15
SLS	5	5	5
Eudragit L100-55	10	10	10
Magnesium Stearate	0.5	0.5	0.5

Example 5

Canine PK Studies on Formulations from Example 4. Table 4 and Example 1. (SLI530CR-F)

Six male beagle dogs were dosed orally with the formulations in the order given in Table 6. Blood was drawn over a 24 Hr period and blood samples were analyzed by HPLC. A noncompartmental analysis of the data was used to generate T_{max}, C_{max}, AUC_{last}, and AUC_{inf}. Relative Bioavailability was calculated in Excel using the AUC_{last} and AUC_{inf} for the CRf formulation as the control. The PK profiles for oxcarbazepine and 10-hydroxycarbazepine are given in FIGS. **7** and **8**.

TABLE 6

Prototypes tested in dogs

Phase	Test Article	SLI Lot #	Dose (mg)
1	Oxcarbazepine CR	PD0294-024A	600
2	Oxcarbazepine CRe	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

TABLE 7

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
T_{max}	1.5	1.8	1.7
C_{max}	1.20	1.72	0.7

TABLE 7-continued

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
AUC_{last}	3.44	7.98	3.41
AUC_{inf}	3.74	11.09	4.01
Rel BA_{last}	101%	234%	100%
Rel BA_{inf}	93%	276%	100%

Example 6

In Silico Modeling of Various Release Profiles of Oxcarbazepine XR

In silico modeling was carried out for various hypothetical systems. Results are shown in FIGS. **9-11**.

Example 7

Human Pharmacokinetic Evaluation of Solubility Enhanced Oxcarbazepine CR Formulations from Example 4

The three solubility enhanced prototypes from the Example 4 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 300 mg) given BID was used as a reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 8 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. **12** and **13**.

TABLE 8

Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal ™

PK Parameters	CRe-F Fast	CRe-M Med	CRe-S Slow	Trileptal ™ BID
T_{max} (Hr)	9	11	14	16
C_{max} (ug/mL)	5.32	5.14	4.40	6.23
AUC_{last} (Hr * ug/mL)	160.3	161.3	148.9	167.1
Rel BA	96%	97%	89%	100%

What is claimed is:

1. A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:

(a) oxcarbazepine;

(b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;

(c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and

(d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhy-

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

SUPERNUS PHARMACEUTICALS, INC., Plaintiff, v. ACTAVIS, INC., et al., Defendants.	Civil No. 13-cv-4740 (RMB/JS)
SUPERNUS PHARMACEUTICALS, INC., Plaintiff, v. ACTAVIS, INC., et al., Defendants.	Civil No. 14-cv-1981 (RMB/JS) **AMENDED ORDER**

The Court having reviewed the parties' submissions and having conducted a Markman hearing,

IT IS ON THIS **7th** day of **MAY** **2015**, **ORDERED** that the Court construes the disputed claims, as to all patents, as follows:

1. "Homogeneous matrix" is defined as a "matrix in which the ingredients or constituents are uniformly dispersed."
2. "Steady state blood level" means "concentration in blood once steady state is achieved."

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUPERNUS PHARMACEUTICALS, INC., **Plaintiff,** **v.** **TWI PHARMACEUTICALS, INC. AND TWI INTERNATIONAL LLC (d/b/a TWI PHARMACEUTICALS USA),** **Defendants.**	**Civil Action No. 15-369 (RMB)(JS)** **(Filed Electronically)**

[~~PROPOSED~~] STIPULATION AND ORDER REGARDING CLAIM CONSTRUCTION